Tetrahedron Letters, Vol.31, No.6, pp 789-792, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

EFFICIENT SYNTHESIS OF PORPHYRIN DIMERS WITH CARBON-CARBON LINKAGES

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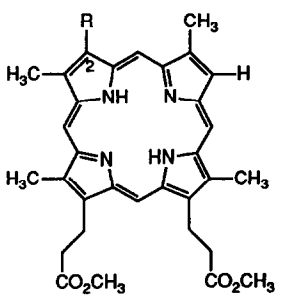
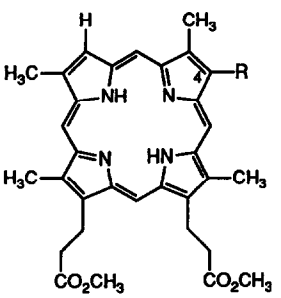
Abstract: *Porphyrin dimers with carbon-carbon linkages were synthesized in excellent yield from (1-hydroxyethyl)-porphyrins by treatment with triflic acid under mild reaction conditions. The method is used to prepare dimers which show promising tumorcidal activity in photodynamic therapy.*

Photodynamic therapy (PDT) involves the action of light on a photosensitizer retained in malignant or other diseased tissue.[1] Application to treatment of cancer mainly depends upon retention of the photosensitizer in the tumor, low systemic toxicity, and the ability of activating light to reach the diseased site.[2] Currently, Photofrin-II® is the only drug being evaluated in phase III clinical trials for treatment of obstructive endobronchial tumors, esophageal tumors, and superficial bladder tumors. Photofrin-II® is a purified form of hematoporphyrin derivative (HpD) which is prepared from hematoporphyrin IX dihydrochloride in two steps by following Lipson's procedure[3] as modified by Dougherty et al. HPLC analyses show that Photofrin-II® is a complex mixture of porphyrins; in recent years a number of studies have been reported and it is believed that Photofrin-II® is a mixture of porphyrin dimers and higher oligomers joined by ether, ester, and carbon-carbon linkages.[4-8]



(1) R = CH(OH)CH$_3$
(3) R = CO.CH$_3$

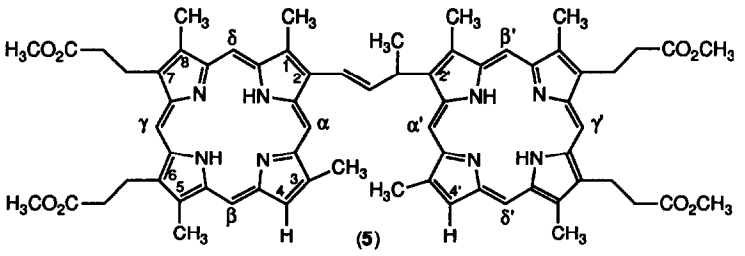


(2) R = CH(OH)CH$_3$
(4) R = CO.CH$_3$

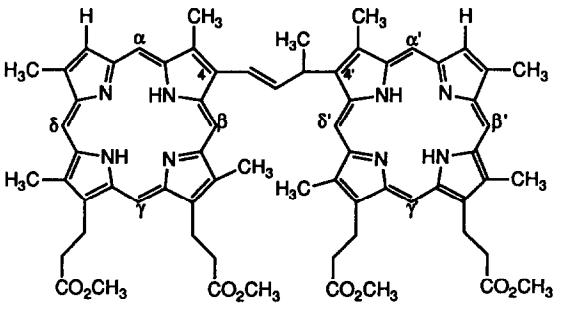
It has been observed that hematoporphyrin dimers with ether or ester linkages are not efficient in vivo photosensitizers, probably due to poor retention in tumors;[9,10] however, ether dimers in which the (1-hydroxyethyl) groups are replaced by vinyl or hydrogen have increased photosensitizing ability.[11,12] In order to investigate the importance of the linkage in such dimers we have developed, and report here, an efficient synthesis of a series of porphyrin dimers linked by carbon-carbon bonds.

Our starting materials were 2-(1-hydroxyethyl) (**1**) and 4-(1-hydroxyethyl) (**2**) deuteroporphyrin IX dimethyl esters, obtained by sodium borohydride reduction of the corresponding isomerically pure 2- and 4-acetyldeuteroporphyrin IX dimethyl esters (**3**) and (**4**),[13] respectively. Simple reaction of (**1**) [or (**2**)] with trifluoromethanesulfonic acid (triflic acid; Aldrich) gave the corresponding dimer (**5**) [or (**6**)] in greater than 90% yield. In a typical experiment, porphyrin (**1**) was dissolved in dichloromethane and stirred under

nitrogen at room temperature for 10 min before addition of triflic acid; after 30 min the reaction was shown to be complete by TLC monitoring. Pyridine was added and after a further 30 min stirring the mixture was subjected to a standard aqueous/dichloromethane work-up. After chromatography on silica gel, the NMR spectrum (Figure 1) indicated clean formation of the dimer (**5**), as attested by a 4.6 Hz coupling constant between the CH=C<u>H</u>-C<u>H</u>(CH_3) protons.



(**5**)



(**6**)

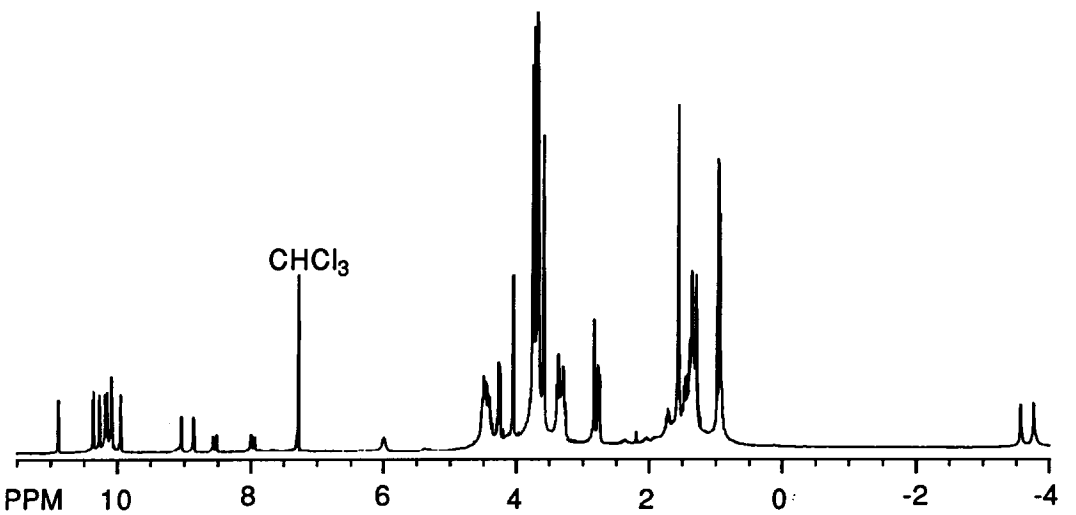
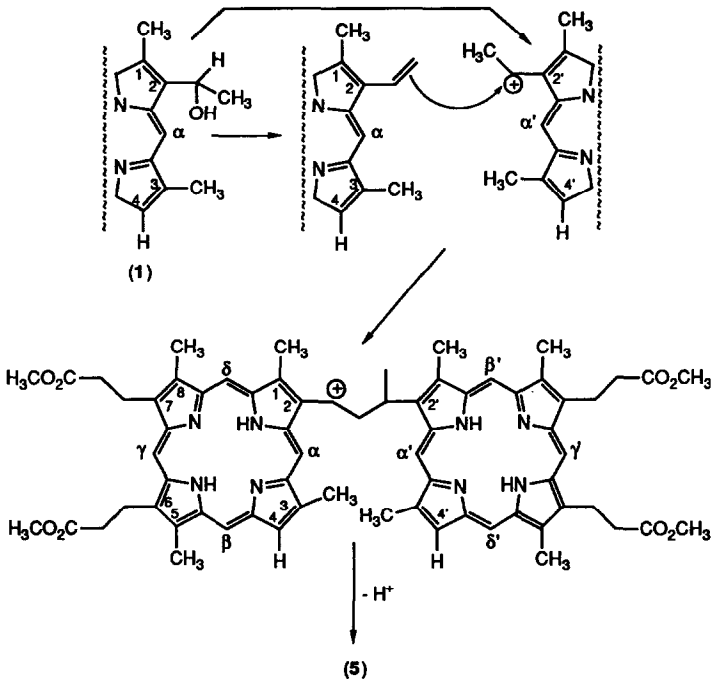


***Figure 1**: 300 MHz Proton NMR spectrum of dimer (5)*

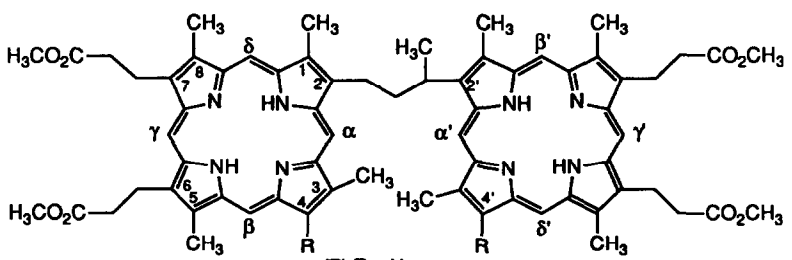
In the proton NMR spectra of both dimers (**5**) (Figure 1) and (**6**), one meso-proton was observed to be downfield of the other seven; this was definitively assigned as the α'-proton in (**5**) and the δ' proton in (**6**), by nuclear Overhauser enhancement (NOE) studies in which irradiation of the low-field meso-proton in (**5**) resulted in a NOE to the bridging C<u>H</u>-CH_3; in (**6**), irradiation of the C<u>H</u>-CH_3 proton gave a NOE to the δ' meso proton.

Scheme 1 shows our proposed mechanism for the formation of dimer (5) from (1).



Scheme 1: Mechanism for formation of Dimer (5) from (1).

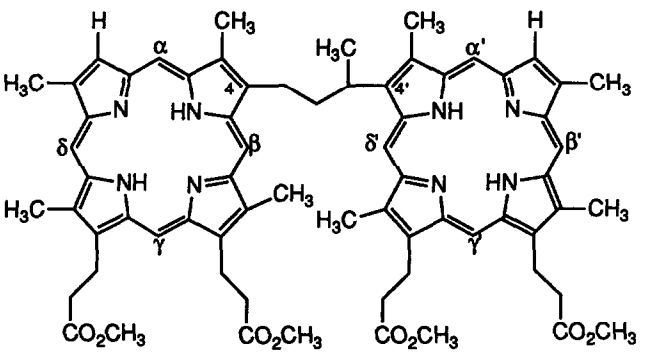
In order to obtain carbon-carbon linked dimers with fully saturated bridging moieties, compounds (5) and (6) were subjected to catalytic hydrogenation. Reduction of the zinc(II) complex of (5) over 10% Pd-C at atmospheric pressure, or at 50 psi, failed to reduce the inaccessible bridging double bond, but use of Raney nickel resulted in smooth formation of a chlorin (λmax 616 nm), which was shown by preliminary NMR experiments to be a mixture in which the bridging carbon-carbon double bond had been saturated. Titration of this mixture with 2,3-dichloro-5,6-dicyanobenzoquinone followed by removal of zinc(II) smoothly afforded the saturated dimers (7) [from (5)] and (8) [from (6)].



(7) R = H
(9) R = CO.CH$_3$
(10) R = CH(OH)CH$_3$
(11) R = CH=CH$_2$

Preliminary biological testing for tumorcidal activity was performed as described previously.[14] The tetra-carboxylic acid dimer from (6) was found to be more active than that from (5). Somewhat surprisingly, the reduced dimers from hydrolysis of (7) and (8) were less active than their unsaturated precursors.[15] In our previous experience of

dimers with ether linkages, manipulation of peripheral substituents [e.g. 1-(hydroxy)ethyl ⇒ vinyl] has made a remarkable difference in PDT efficacy.[16] We are therefore currently synthesizing dimers such as (**9**)-(**11**), and similar derivatives from (**5**), (**6**), and (**8**), using standard chemistry,[17] and this work will be reported in our full paper.



(**8**) R = H

Acknowledgments: K.M.S. thanks the National Institutes of Health (HL 22252) and the National Science Foundation (CHE-86-19034) for support of this research. C.J.M. is grateful to the Fulbright Commission for a Travel Scholarship.

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(Received in USA 8 November 1989)